BIOBEHAVIORAL PAIN RESEARCH

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P.T.

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National Institute of Dental and Craniofacial Research
National Institute on Aging
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Cancer Institute
National Institute of Child Health and Human Development
National Institute on Drug Abuse
National Heart, Lung, and Blood Institute
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Center for Complementary and Alternative Medicine

This program announcement replaces PA-95-056, which was published in the NIH Guide, Vol 24, No. 15, April 28, 1995.

PURPOSE

The purpose of this biobehavioral pain research program announcement (PA) is to inform the scientific community of the interests of the various institutes at the National Institutes of Health (NIH) and to stimulate and foster a wide range of basic and clinical studies on pain as they relate to the missions of these Institutes.

Applications are encouraged to study individual differences in pain responses which may be due to factors such as genetic differences, endocrine activity, neural activity, immune function, psychological state, disability state, age, gender, and cultural background. Research is also needed in areas such as understanding the neuroanatomical pathways and the europhysiological mechanisms in pain. The pain experience needs to be examined at all levels of research including the gene, molecule, cell, organ, and individual with the goal of developing biobehavioral interventions to manage or prevent pain.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS led national activity for setting priority areas. This Program Announcement (PA), Biobehavioral Pain Research, is related to the priority areas of chronic disabling conditions, cancer, and clinical prevention services. Potential applicants may obtain a copy of "Healthy People 2000" at http://www.crisny.org/health/us/health7.html.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) research project grant (R01) award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this PA may not exceed five years.

RESEARCH OBJECTIVES

Pain is a critical national health problem. It is the most common reason for medical appointments, nearly 40 million visits annually, and costs this country over $100 billion each year in health care and lost productivity. Pain has a profound effect on the quality of human life. In addition to possible deleterious effects on immune function, pain can cause disruptions in sleep, eating, mobility, and overall functional status. In the hospitalized patient, pain may be associated with increased length of stay, longer recovery time, and poorer patient outcomes, all of which have health care quality and cost implications.

Progress is being made in understanding the neuroanatomical pathways and the neurophysiological and neurochemical mechanisms involved in pain. However, understanding

the subjective pain experience in individuals presents unique scientific challenges. Even though the basic physiology may be similar, people react in very different ways, perhaps due to genetic differences, endocrine activity, neural activity, immune function, stress, psychological state, age, gender, and cultural background. Thus, the pain experience needs to be examined at all levels of basic and clinical research, including the gene, molecule, cell, organ, and individual, with the goal of developing biobehavioral interventions to manage or prevent pain.

In order to develop a research agenda, ten NIH institutes sponsored a workshop, "Biobehavioral Pain Research: A Multi-Institute Assessment of Cross-Cutting Issues and Research Needs," in January 1994. This meeting, under the aegis of the NIH Health and Behavior Coordinating Committee, resulted in the identification of research needs from a broad spectrum of the scientific community expert in pain research.

The following pain research areas cut across Institutes and programs and should not be viewed as restricted to only one specific Institute. Current NIH referral guidelines will be used to assign grant applications to the most appropriate NIH Institute based on the scientific focus of the application.

The following topics and study areas are not intended to be comprehensive or exclusive:

Understanding Critical Interfaces Between Biology and Behavior

o Explore the neural basis of pain perception and discover targets in the signal transduction pathways that may be the most effective points for interventions in the control of pain across the lifespan.

o Examine the neuroendocrine and immunological correlates of pain.

o Investigate both pharmacological and behavioral interventions to prevent pain.

o Refine neuroimaging algorithms for the study of structural and functional correlates of pain perception.

o Conduct animal and human studies on the temporal patterning of pain.

o Explore the basic developmental aspects of pain processing, including an integration of psychological, neurochemical, and molecular approaches which could impact the treatment of pain across the life span.

o Identify genes relevant to pain and pain inhibitory mechanisms.

o Examine the role of placebo effect in pain treatment.

Pain, Suffering, and Emotion

o Explore basic mechanisms of the conscious perception of pain and the affective responses to pain.

o Examine the relative importance of biological, socioenvironmental, and psychological variables in explaining variations in pain-expressive behaviors.

o Clarify the relationship between depression and chronic pain by elucidating the biological factors, characteristics of the pain (e.g., location, quality, timing), environmental circumstances, and personal characteristics that are predictive of this relationship.

o Elucidate emotions and emotional disturbances, in addition to depression, (e.g., anger, fear, anxiety) which are associated with acute and chronic pain conditions, and determine how these emotions modify the experience of pain.

Pain and Behavior

o Explore the sensory, cognitive, and affective aspects of acute and chronic pain across the lifespan.

o Elucidate the interaction of biological markers, central nervous system mechanisms, and drug and behavioral interventions.

o Determine the relative contributions of biological, psychological, behavioral, and environmental predictors of the course of pain, pain dysfunction, and response to treatment for pain.

o Examine addiction risk in patients taking controlled drugs for pain; the role of tolerance, addiction and dependence in the consumption of these drugs; and implications of long-term use in noncancer disease states.

o Develop and refine biobehavioral techniques for optimizing adherence to pain management.

Behavior-Related Interventions

o Evaluate research strategies to integrate medical, nursing, dental, neurological, pharmacological, and behavioral treatments for pain problems. Compare the relative effectiveness of each mode of treatment, and combined treatments, and their potentiating effects on multiple outcomes, such as pain, physical functioning, psychological functioning, health care utilization, and costs.

o Conduct research on the mechanisms and process variables that are responsible for the efficacy of behavioral interventions. This research includes studies to understand better the effect of patients' expectations and beliefs, psychophysiological states (e.g., anxiety, relaxation, stress), adherence, and specific cognitive (e.g., imagery) and social (e.g., support) components in behavioral interventions.

o Determine which behavioral treatments are most effective for specific subgroups of patients differentiated by factors such as age, gender, race, ethnic group, level of dysfunction, or psychosocial characteristics.

o Conduct clinical trials of cognitive/behavioral pain control methods and combinations of medical, pharmacological, and cognitive/behavioral pain control methods.

o Compare the costs of various types of interventions for pain, including economic analyses of pain, pain dysfunction, and pain treatments with different and combined biomedical and biopsychosocial models of treatment.

o Investigate the effectiveness and appropriate targeting of alternative treatments (e.g., hypnosis, massage, spinal manipulations, acupuncture) using randomized, controlled trials of these treatments in association with conventional medical approaches.

o Assess methods for primary, secondary, and tertiary prevention of pain.

o Establish dose-response curves for biobehavioral interventions.

o Test interventions to improve health care practice in such areas as pain assessment, analgesic management, pain prevention, and rehabilitation.

Commonalities and Differences in Pain Expression, Experience, and Treatment

o Study cognitive factors in the experience of pain, disability, and pain behaviors across disorders, including such factors as self-efficacy, perceived control, and pain beliefs.

o Establish the factors that prevent a person with acute pain from developing a chronic pain problem and a chronic pain- related disability. Areas to assess include patient biological/organic, psychosocial, and socioeconomic characteristics, interactions of the patient with health care providers, family and social supports, and workplace factors.

o Refine existing techniques for measuring pain and develop new techniques that are disease- and outcome-specific for different populations.

o Determine the supraspinal mechanisms of pain modulation, determine the effects of specific pain treatments on these central nervous system processes, and apply new findings on CNS plasticity to the understanding of pain.

o Examine the interrelationships between pain and other symptoms and comorbidities (e.g., fatigue, sleep alterations, nausea, vomiting, anxiety, mood disorders, physical deconditioning, stress).

Pain in Special Populations

o Test culturally sensitive approaches to pain assessment and management, including translation of the instruments into foreign languages and validation as needed.

o Investigate biobehavioral pain treatments for special populations including infants, children, elderly, cognitively impaired, ethnic minority groups, substance abusers with pain disorders, and individuals with disabilities.

o Determine effective biobehavioral interventions for HIV- and AIDS-related pain, as well as the pain prevalence, scope, and severity of patients who are HIV-infected. Explore alterations in nociceptive mechanisms and pain perception in patients with HIV.

o Investigate the roles of sleep and circadian variation in the precipitation and modulation of pain in populations who have special rest - activity needs such as infants, children, elderly, pregnant women, night-shift workers. This research could include studies of the effect of pain and its pharmacological treatment on sleep and daytime alertness, as well as the effects of disturbed sleep on pain and pain perception. Studies of seasonal and other variations are also appropriate.

o Test and evaluate pharmacotherapies and behavioral treatments in patients with current and past histories of addiction, including infants born to drug-, alcohol-, and tobacco-dependent mothers, and HIV-infected persons.

o Investigate the effectiveness of biobehavioral pain management in terminally ill and dying patients.

o Study the interrelationship of Axis II, as well as Axis I, psychiatric disorders (e.g., borderline personality, histrionic, antisocial) and chronic pain, and relate these findings to pharmacological and behavioral therapies.

o Determine gender-related differences in the pain experience, such as whether the experience of clinical chronic pain varies during the menstrual cycle and, if so, the hormonal, immunological, neuronal, and psychological correlates of this variability.

o Investigate biobehavioral approaches to managing pain associated with acute and chronic illness such as arthritis, cancer, diabetes, sickle cell disease, low back pain, headaches, temporomandibular disorders, and other orofacial pain conditions.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994 available on the web at the following URL address: http://www.nih.gov/grants/guide/notice-files/not94-105.html

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://www.nih.gov/grants/guide/notice-files/not98-024.html

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.4/98) and will be accepted at the standard application deadlines indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: GrantsInfo@nih.gov.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e, as plans for the study are being developed. Furthermore, the application must obtain agreement from the IC staff that the IC will accept the application for consideration for award.

Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://www.nih.gov/grants/guide/notice-files/not98-030.html

Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

The initial review group will also examine the provisions for the protection of human subjects and the safety of the research environment.

Additional scientific/technical merit criteria specific to the objectives of the RFA and the mechanism used must be included if they are to be used in the review.

AWARD CRITERIA

Applications will compete for available funds with all other approved applications. The following will be considered in making funding decisions: Quality of the proposed project as determined by peer review, availability of funds, and program priority.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.361, 93.121, 93.866, 93.846, 93.399, 93.865, 93.279, 93.838, 93.242, 93.855, and 93.213. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, and portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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